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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,343	01/30/2006	Andrzej Lipkowski	7444/73871/GJG	4648

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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
12/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,343	LIPKOWSKI ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-9 and 11-16* is/are pending in the application.

4a) Of the above claim(s) *11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3 and 5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-final rejection filed on October 29, 2007 is acknowledged. Claims 2-3, 5-9 and 11-16 are pending in this application. Applicant elected with traverse Group I (claims 2-3 and 5-9) and elected species (Tyr-D-Met-Gly-Phe-NH-)$_2$ on April 9, 2007. Applicant's arguments were not found persuasive and the Restriction requirement was deemed proper and made Final in the previous office action mailed on June 26, 2007. Claims 11-16 remain withdrawn from further consideration as being drawn to nonelected invention. Claims 2-3 and 5-9 are examined on the merits in this office action.

Julie Ha is the Examiner of record.

Withdrawn Objections and Rejections

1. Objection to specification is hereby withdrawn due to Applicant's amendment to the specification.

2. Objection to claims 2-3 and 5-9 are hereby withdrawn due to Applicant's amendment to the claims.

3. Rejection to claims 2-3 and 5-9 under 35 U.S.C. 112, 2nd paragraph is hereby withdrawn due to Applicant's amendment to the claims.

Maintained Rejection

35 U.S.C. 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 2-3 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai et al (Biochem. Biophys. Res. Comm., 1979, 91: 1239-49) in view of Abbruscato et al (J. Neurochem., 1997, 69: 1236-45) and Kanai et al (J. Biol. Chem., 1998, 273: 23629-32).

8. Ronai et al teach the tetrapeptide-amide analog of enkephalin H-Tyr-D-Met-Gly-Phe-NH_2 and its opioid activity in guinea pig ileum (abstract). The difference between the reference and the instant claims is that the reference does not teach the elected species (Tyr-D-Met-Gly-Phe-NH-)$_2$.

9. However, Abbruscato et al teach the compound biphalin, (Tyr-D-Ala-Gly-Phe-NH-)$_2$, an opioid peptide containing two pharmocophores linked by a hydrazine bridge. When administered intracerebroventricularly, biphalin has been shown to be more potent than morphine and capable of crossing the blood-brain barrier (see abstract). Abbruscato et al attribute this potency in part to the affinity of the large neutral amino acid carrier for biphalin (see p. 1244, first column). Kanai et al teach that the large neutral amino acid carrier has affinity for methionine (see p. 23629, second column).

10. Therefore, it would have been obvious to one of ordinary skill in the art to substitute methionine for the alanine in biphalin taught by Abbruscato et al in order to mimic the tetrapeptide taught by Ronai et al, satisfying all of the limitations of claim 2. With respect to claim3, Abbruscato et al teach biphalin in combination with pharmacologically acceptable carrier, in the form of an aqueous saline solution, and formulated for direct application to the site of analgesic activity including the CNS (see p. 1237). The skilled artisan would have been motivated to make this substitution given that the large neutral amino acid carrier has a greater affinity for methionine than alanine and that the affinity of this receptor for biphalin is responsible in part for biphalin's potency. There would have been reasonable expectation of success given that the tetrapeptide harboring methionine instead of alanine has opioid activity. Thus,

the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

11. Applicant argues that "Ronai et al does not teach a compound comprising two peptides linked by a hydrazine bridge at their C-termini, and instead teaches that any alteration of the C-terminus 'drastically' alters their binding ability". Further, Applicant argues that "in view of this unpredictability, one of ordinary skill in the art, would have no reasonable expectation of success of the claimed composition which possess a considerable alteration of the C-terminus. Further, Applicant argues that Kanai et al "teaches that the transporter is inhibited by the isomer D-Methionine". Therefore, Applicant argues that "one of ordinary skill in the art would not be motivated to replace the D-Alanine of the peptide taught by Abbruscato et al with a D-Methionine". Additionally, Applicant argues that "there is no reasonable expectation that the peptide comprising the D-Methionine would be an analgesic peptide".

12. Applicant's arguments have been fully considered but have not been found persuasive because Ronai et al teach that changing the C-terminal amino acid for a cyclic imino acid dramatically decreases the agonist potency in MVD but not in GPI. Amidation of terminal imino acid brings about a further fall in potency in MVD and significant increase in GPI. Removal of the fifth residue/the C-terminus is still amidated/ leads to a loss in activity in MVD and to an enhancement in GPI. Applicant has focused on the sentence "amidation at the C-terminus alters drastically the binding properties of an enkephalin analogue per se" (see p. 1245). However, this sentence is not a negative

implication. A "drastic" alteration in the binding properties can mean both "increasing" and "decreasing" the binding properties. Applicant has focused solely on the mouse model. However, Ronai et al clearly indicate "decrease of potency in MVD but not in GPI"; "fall in potency in MVD and significant increase in GPI"; "loss of activity in MVD and to an enhancement in GPI". This indicates that the enkephalin agonists are specific towards different species. Therefore, one would be motivated to modify the C-terminus of the peptide and make a dimeric peptide analog of enkephalin that contains two pharmacophores lined by a hydrazide bridge, since Abbruscato et al teaches that (Tyr-D-Ala-Gly-Phe-NH-)$_2$ was the most potent analgesic enkephalin analog that was studied to date. Kanai et al teach that the large neutral amino acid carrier has affinity for methionine, and since Ronai et al teaches the monomeric sequence (Tyr-D-Met-Gly-Phe-NH_2) showed significant increase in potency (alters drastically the binding properties of an enkephalin analog), and Abbruscato et al showed that dimeric peptide analog of enkephalin linked by a hydrazide bridge had the most potent activity, it would have been obvious to substitute Met for Ala, to see what effect it would have on the analog potency and transport system. There is a reasonable expectation of success, since both Ronai and Abbruscato references teach enkephalin analogs that showed significant increase in potency. Therefore, the rejection is maintained.

13. Claims 2-3 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai et al (Biochem. Biophys. Res. Comm., 1979, 91: 1239-49), Abbruscato et al (J. Neurochem., 1997, 69: 1236-45) and Kanai et al (J. Biol. Chem., 1998, 273: 23629-

32) as applied to claims 2-3 and 6-8 above in further view of Hill (US Patent # 5880132), Bock et al (EP 0434369 A1) and Ornstein (US Patent # 5356902).

14. Ronai et al, Abbruscato et al and Kanai et al do not teach the administration of (Tyr-D-Met-Gly-Phe-NH-)$_2$ in combination with compounds that block stimulatory amino acid, tachykinin or cholecystokinin receptors (claim 5) or in combination with biphalin.

15. Ornstein teaches stimulatory amino acid antagonists, decahydroisoquinoline compounds, and their use as analgesic compounds (column 2, lines 6 and 7). Hill teaches pharmaceutical compositions comprising both piperidine tachykinin antagonist and opioid analgesics (abstract). Bock et al teach cholecytokinin antagonists and their ability to potentiate morphine and other analgesics.

16. Therefore, it would have been obvious to one of ordinary skill in the art to combine the (Tyr-D-Met-Gly-Phe-NH-)$_2$ analgesic taught by combination of Ronai et al, Abbruscato et al and Kanai et al and the stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists taught by Ornstein, Hill and Bock et al or the biphalin taught by Abbruscato et al. The skilled artisan would have been motivated to do so given that the prior art teaches that compounds such as (Tyr-D-Met-Gly-Phe-NH-)$_2$ and biphalin have the same or complimentary functions as stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists. There would have been a reasonable expectation of success given that the stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists and their pharmaceutical use are well-known in the prior art and compatible with opioid analgesics. The MPEP states in section 2144.06: "It is prima facie obvious to combine two compositions each of which is taught by the prior

art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)" Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

17. Applicant argues that "Ronai et al does not teach a compound comprising two peptides linked by a hydrazine bridge at their C-termini, and instead teaches that any alteration of the C-terminus 'drastically' alters their binding ability". Further, Applicant argues that "in view of this unpredictability, one of ordinary skill in the art, would have no reasonable expectation of success of the claimed composition which possess a considerable alteration of the C-terminus. Further, Applicant argues that Kanai et al "teaches that the transporter is inhibited by the isomer D-Methionine". Therefore, Applicant argues that "one of ordinary skill in the art would not be motivated to replace the D-Alanine of the peptide taught by Abbruscato et al with a D-Methionine". Additionally, Applicant argues that "there is no reasonable expectation that the peptide comprising the D-Methionine would be an analgesic peptide". Applicant further argues that "the teachings of Hill et al, Bock et al, and Ornstein, in combination with the remaining cited art, do not cure the deficiency (stated above). The combination Of reference does not teach or suggest (Tyr-D-Met-Gly-Phe-NH-)$_2$, and does not teach or suggest Applicants' invention".

18. Applicant's arguments have been fully considered but have not been found persuasive because the prior arts combined teach or suggest Applicant's invention. Response to Applicant's arguments for Ronai, Abbruscato and Kanai references are stated above. As discussed above, Ornstein teaches stimulatory amino acid antagonists, decahydroisoquinoline compounds, and their use as analgesic compounds (column 2, lines 6 and 7). Hill teaches pharmaceutical compositions comprising both piperidine tachykinin antagonist and opioid analgesics (abstract). Bock et al teach cholecytokinin antagonists and their ability to potentiate morphine and other analgesics. Since stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists and their pharmaceutical use are well-known in the prior art and compatible with opioid analgesics, there is a reasonable expectation of success and motivation to combine the teachings. Therefore, the rejection is maintained.

New Objections-Minor Informalities

19. The abstract is objected to because of the following informalities: There appears to be grammatical errors in the abstract. At line 2 (right below the compound structure), it recites "wherein R_1 a D-alanine..." and at line 3, it recites "...D-glutamine side chain and is a R_2 is a..." The word "is" appears to be missing from line 2 and "is a" from line 3 appears to be an error. Applicant is advised to correct these errors.

20. Claim 2 is objected to because of the following informalities: There appears to be grammatical errors in the abstract. At line 13 (right below the compound structure), it recites "wherein R_1 a D-alanine..." and at line 14, it recites "...D-glutamine side chain

and is a R_2 is a..." The word "is" appears to be missing from line 13 and "is a" from line 14 appears to be an error. Applicant is advised to correct these errors.

Conclusion

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claims are allowed.

22. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

24. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

25. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

12/10/10
ANISH GUPTA
PRIMARY EXAMINER

Julie Ha
Patent Examiner
AU 1654